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Brief Clinical Report

Clinic-Based Study of Plexiform Neurofibromas in Neurofibromatosis 1

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Individuals with neurofibromatosis 1 (NF1) develop both benign and malignant tumors at an increased frequency. One of the most common benign tumors in NF1 is the plexiform neurofibroma. These tumors cause significant morbidity and mortality on account of their propensity to grow and affect adjacent normal tissues. To determine the clinical profile of plexiform neurofibromas in NF1, we conducted a retrospective review of 68 NF1 patients with plexiform neurofibroma. In our series, 44% of tumors were detected by 5 years of age and most were located in the trunk and extremities. Only two patients developed malignant peripheral nerve sheath tumors in their preexisting plexiform neurofibromas. Lastly, we demonstrate that there were no specific clinical features of NF1 associated with the presence of plexiform neurofibroma. These results underscore the importance of careful serial examinations in the evaluation of patients with NF1. Am. J. Med. Genet. 92:132–135, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: neurofibromatosis 1; plexiform neurofibroma; cancer; tumor

INTRODUCTION

Neurofibromatosis 1 (NF1) is a common autosomal dominant disorder with variable clinical manifestations and an unpredictable course [Huson et al., 1988]. One of the hallmarks of NF1 is an increased propensity for developing both benign and malignant tumors [Hope and Mulvihill, 1981; Gutmann et al., 1997]. One of the most common benign tumors in individuals with NF1 is the discrete neurofibroma, a tumor composed of Schwann cells, fibroblasts, perineural cells, and mast cells. These tumors are always benign and are not associated with malignant transformation. In contrast, a subtype of neurofibroma, termed a plexiform neurofibroma, can undergo malignant transformation and represents a significant health concern. Plexiform neurofibromas are classified as benign peripheral nerve sheath tumors that involve multiple nerve fascicles or branches of major nerves. They often affect cranial nerves V, IX, and X and can be detected both in superficial and in deep nerve sheaths [Krueger et al., 1979; Chow et al., 1993; Ferguson and Kyle, 1993]. Plexiform neurofibromas are often poorly circumscribed, locally invasive, nonmetastatic tumors variably composed of Schwann cells, fibroblasts, and other cell types [McCarron and Goldblum, 1998]. These tumors often lead to soft tissue overgrowth and cause dysfunction, pain, and disfigurement. Moreover, in individuals affected with NF1 there is a 2–5% risk of malignant peripheral nerve sheath tumor development (MPNST) [Hope and Mulvihill, 1981; Bader 1986].

Several clinic-based series of patients with NF1 have been reported but none have specifically examined plexiform neurofibromas [Huson et al., 1988; Riccardi, 1992; Friedman et al., 1993; North, 1993]. To better characterize the clinical features of patients with NF1 and plexiform neurofibromas, we conducted a retrospective review of NF1 patients with plexiform neurofibroma seen in a tertiary care referral center. In this study, we present information about the clinical features of plexiform neurofibromas in NF1 with specific regard to the location of tumors, age of presentation, and presenting symptoms.

METHODS

The Neurofibromatosis Program at St. Louis Children's Hospital (Washington University School of

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Medicine) and Cardinal Glennon Children's Hospital (St. Louis University) meet regularly and are attended by members of the Departments of Neurology and Medical Genetics. Ophthalmology and Dermatology clinics are held on the same day and are easily accessible for evaluation. Other services are readily available for consultation, including Oncology and Neurosurgery.

Patients are referred from the surrounding states by health care practitioners for initial evaluation and long-term follow-up. Four hundred and five individuals were evaluated for NF1 and 74 patients with plexiform neurofibroma were identified. Of these, six patients presented with only a plexiform neurofibroma and did not meet diagnostic criteria for NF1 and were excluded from the review. The charts and medical records from the remaining 68 patients were reviewed. All patients were examined by one of the authors and a diagnosis of plexiform neurofibroma was based on the findings of a diffuse, nondiscrete tumor on physical examination. Pathology reports were obtained for all patients who had undergone biopsy or surgical resection to histologically confirm the diagnosis of plexiform neurofibroma. MRI and CT scans of patients who did not have pathological diagnosis were reviewed for radiographic findings consistent with plexiform neurofibroma.

RESULTS AND DISCUSSION

Sixty-eight of 405 patients (16.8%) evaluated with a diagnosis of NF1 harbored 74 plexiform neurofibromas. This is in accordance with previously reported frequencies in the clinic-based series cited above of plexiform neurofibroma varying from 16–40%. The gender distribution of the cohort was comparable with 38 male patients and 30 female patients. The frequency of common characteristics associated with NF1 in this group was similar to those previously reported (Table I) [North, 1993]. The presence of a plexiform neurofibroma did not correlate with any specific feature of NF1.

Six of the patients (9%) with plexiform neurofibroma had more than one tumor. Previous reports found multiple plexiform neurofibromas in 12.5–21% of patients [Huson and Hughes, 1994; Friedman and Birch, 1997]. All six of the patients reported here had two plexiform neurofibromas at different sites and did not include plexiform neurofibromas that recurred at resected sites. Two patients were found to harbor two separate tumors at the time of diagnosis; one with a tumor of the eyelid and of the thoracic spine and another with a tumor involving the cheek/face as well as the leg. Four patients had an additional tumor discovered subsequent to the time of diagnosis of the first tumor; one patient with a tumor of the orbit at 3 years of age and a second of the sacrum at 4 years of age; one patient with a tumor of the orbit at 3 years and one tumor of the lumbar spine at 9 years; one patient with a tumor of the face at 5 years of age and a retroperitoneal tumor at 13 years of age; and one patient with a tumor of the hip/thigh at 5 years of age and one tumor of the chest cavity at 14 years of age. There were no clinical characteristics that distinguished those patients with two plexiform neurofibromas from those patients with single tumors.

Learning disability, defined as developmental delay or learning difficulties such as attention deficit disorder, decreased visual motor coordination, and language deficits requiring therapy occurred in 40% (27/68) of the patients, which is similar to the frequency reported by North [1993]. No patients in this group had either severe developmental delay or mental retardation.

Plexiform neurofibromas can become symptomatic at an early age and continue to grow throughout a patient's life [Krueger et al., 1979]. The age at diagnosis of a plexiform neurofibroma in these 68 patients is shown in Table II. Predicting the precise age at which the tumor first developed was difficult; however, six patients were noted to have plexiform neurofibromas at birth and all six had tumors of the head and neck region. Seventeen percent (12/72) of the tumors were diagnosed in the first year of life, six of these noted at birth. Two of these 12 patients (17%) did not fulfill diagnostic criteria for NF1 at the time of diagnosis of their plexiform neurofibroma, but did meet criteria later in life. In addition, 44% (32/72) were diagnosed before 5 years of age. This early age at diagnosis supports the idea that plexiform neurofibromas are congenital lesions [Riccardi, 1992]; however, 18% (13/72) presented with a plexiform neurofibroma after age 20 years. Although all of these tumors were reported to have been present for many years, this late age of recognition emphasizes the importance of examining patients with NF1 for these tumors regardless of age.

Plexiform neurofibromas have been reported to occur most commonly on the trunk (44%), followed by the limbs (38%) and the head and neck (18%) [Huson et al., 1988]. The location of the tumors in this cohort is

TABLE I. Clinical Findings of NF1 Seen in Patients With Plexiform Neurofibroma

Clinical features of NF1	Patients with plexiform neurofibroma (n = 68)		North [1993] (n = 200)
	#	%	%
Café-au-lait macules	62	91	95.5
Cutaneous and subcutaneous neurofibromas	45	66	50
Axillary freckling	43	63	84
Inguinal freckling	16	24	52
Lisch nodules	45	66	66
Optic gliomas	8	12	9
Family history	34	50	56
Scoliosis	22	32	21

TABLE II. Age at First Diagnosis of a Plexiform Neurofibroma

Age at presentation	Number of patients
Birth	6
0–6 months	3
6–12 months	3
1–5 years	20
5–10 years	16
10–15 years	6
15–20 years	5
20–25 years	6
>25 years	7

TABLE III. Location of Plexiform Neurofibromas and Presenting Symptoms

Location of plexiform neurofibroma	Number of patients	Presenting symptoms
Abdomen (peritoneal and retroperitoneal)	6	Pain, blood in stool
Back (including spine)	10	Leg pain, weakness in extremities
Chest	6	Pain, weakness in extremities, enlarging mass
Extremities		
Lower (excluding hip)	9	Increasing size of mass
Upper	2	
Thigh/hip/perineal (including genitalia)	10	Pain in back and leg, increasing size of mass
Head/face/neck		
Orbit	13	Ptosis, glaucoma, decreased vision, disconjugate gaze
Tongue/oropharynx	3	Speech problems, drooling, jaw and neck pain
Other	15	Compression of airways and esophagus, enlarging mass, hearing loss, pain in face and neck

shown in Table III. The trunk accounted for 43% (32/74), the extremities for 15% (11/74), and the head and neck region for 42% (31/74) of all plexiform neurofibromas.

The presenting symptoms were most often related to increasing size of the mass, an associated loss of function (most commonly weakness), or pain (Table III). Thirty-two percent of patients (22/68) presented with complaints of asymmetry or increasing size of a mass. Thirty-two percent (22/68) presented with pain localized to the area of the tumor or related to neurological complaints of weakness, numbness, or tingling. Eighteen percent of the tumors (13/74) involved the orbit or eyelid and caused symptoms of ptosis, myopia, astigmatism, glaucoma, amblyopia, or decreased vision. Other presenting symptoms included drooling secondary to a large tongue, blood in the stool, airway and esophageal compression, weakness, and hearing loss.

The risk of developing a malignant peripheral nerve sheath tumor in NF1 has been estimated at 2–5% [Bader, 1986; Zoller et al., 1997]. Two patients (3%) in our series developed an MPNST. One of these malignant tumors developed in a 25-year-old male with a preexisting plexiform neurofibroma of the neck. He is alive 18 months after wide resection and local radiation therapy without evidence of recurrence. The other MPNST developed in a 13-year-old girl with a preexisting plexiform neurofibroma of the mid-back with evidence of widespread metastases to bone and lung. She died within 18 months despite complete surgical excision and aggressive chemotherapy.

Nine percent (6/68) of the cohort developed other tumors, including fatty tumors of the ovaries, adult lipoma, benign fibrous tumor, brainstem glioma, fibrosarcoma of the breast, and hepatic adenoma. Although none of these tumors have a specific association with NF1, an increased incidence of malignant and benign tumors in patients with NF1 has previously been reported [Zoller et al., 1997].

The management of plexiform neurofibromas included surgery in 53% (36/68) of the patients. Three patients had biopsy alone, and 43% (29/68) did not have a surgical procedure. Of the 53% with a surgical procedure, 33% were performed because of medical complications related to the tumor and the remaining 66% were performed either for debulking due to size, pain, or cosmetic reasons.

CONCLUSION

Plexiform neurofibroma is a relatively common manifestation of patients with NF1 and can cause significant morbidity and mortality. Reliable information about the epidemiology, presenting symptoms, and long-term outcome, as well as specific findings which identify patients at higher risk for plexiform tumors, is lacking. Many individual case reports and some series examining surgical management exist, but better studies describing tumor characteristics and associated symptomatology are needed.

We present here the results of a review of 68 NF1 patients with plexiform neurofibroma. This study is a retrospective review, which is limited by lack of long-term follow-up. This study represents the largest review of symptoms specifically associated with plexiform neurofibromas where all patients are enrolled from a single large catchment area and all were examined by at least one of the authors. This review suggests that there are no specific findings in NF1 associated with plexiform tumors. The young age at detection and few cases of MPNST development support the view that these tumors are congenital in origin and have a relatively low risk of malignant transformation. In addition, information about location of tumor at the time of presentation, and identification of presenting symptoms assist in raising awareness of the diffuse nature of these tumors. It reinforces the importance of performing serial exams on NF1 patients, with special attention paid to the development of a plexiform neurofibroma.

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